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FELLOWSHIP FINAL REPORT

Coordination compounds as antioxidants: activity evaluation by combining first-principle calculations and solid-state NMR

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ABSTRACT

Inspired by the active site of the copper-zinc superoxide dismutase enzyme, we studied the reactivity of imidazolic ligands to improve the design and synthesis of coordination compounds, active against the superoxide radical (responsible of DNA, cellular and tissues damage, leading to illness like cancer, atherosclerosis, heart failures, etc.). By the joint use of first-principle calculations and solid state NMR spectroscopy, we identified the relationship between the structural characteristics and the reactivity of the synthesized compounds, that lead and modulates their antioxidant activity.

1- Introduction

The increasing number of illness related with the pathological condition known as oxidative stress,^{1,2} such cancer, amyotrophic lateral sclerosis, cardiac failures, diabetes, Alzheimer's and Parkinson's diseases, among others,^{3,4} demands the attention of scientist and pharmaceutical industries, in the design and production of new antioxidant drugs. Those antioxidant drugs should be capable to assist the organism in the modulation of the reactive oxygen species (ROS) concentration, to prevent the developing of diseases related with oxidative stress. At this respect, the joint use of theoretical and spectroscopic tools is indeed, one of the most promising strategies.⁵⁻⁸ An starting and key point, in different drug design strategies, is the structural similitude between

the designed molecule and biological or synthetic active compounds.⁹

One of the most important endogenous antioxidant, is the metalloenzyme known as copper-zinc superoxide dismutase (CuZn-SOD).¹⁰⁻¹³ This metalloenzyme, is present in different cellular compartments and is the first natural defense against the superoxide anion (O_2^-), the first ROS obtained from vital cellular processes as the respiration.^{2,13-15} The CuZn-SOD reduces the toxicity of O_2^- in two steps producing oxygen and hydrogen peroxide (metabolized by other natural enzymes),¹⁶ avoiding the damage to DNA, cellular structures and tissues.

In this project, inspired by the antioxidant relevance of the CuZn-SOD,^{13,16,17} and based on

our experience about the reactivity studies of heterocycles like imidazole,^{18–21} (one of the nitrogenated heterocycles vastly present in biomolecules, and considered for drug design),^{21–23} our objectives were to design coordination compounds, inspired in the active site of CuZn-SOD^{16,17} (**Figure 1**), and to study, by solid state nuclear magnetic resonance (ss-NMR) spectroscopy and first principle calculations, the ability of the designed and synthesized compounds, to react as antioxidants, trapping the superoxide anionic radical.

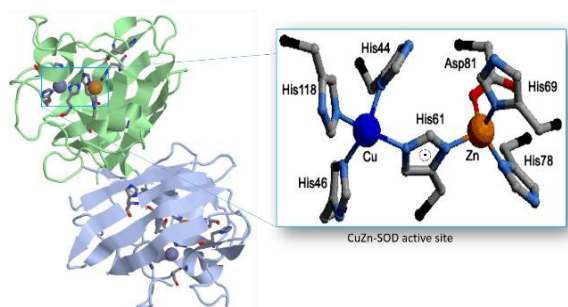


Figure 1. Scheme of the CuZn-SOD dimeric structure and its copper(II)-zinc(II) active site. The copper cation is coordinated by the imidazolic rings from histidine residues 44,46,118, the zinc (II) cation is coordinated to three imidazole rings of histidine residues and one carboxylate from the aspartate 81 residue and both metal cations are bonded to the imidazolite ring from the histidine residue 61. This imidazolite bridge is characteristic of the CuZn-SOD metalloenzyme.

The knowledge that structural information provides leads to improvements for the drug design strategies. At this respect, crystallography is one of the techniques which, based on the electron density of the atoms in the compound, leads to the unequivocal structure of the molecule under study, and provides information about intra and intermolecular interactions.²⁴

In the case of metal containing compounds mimicking the structure of the active sites of metalloenzymes, the presence of transition metals cations reduces the possibility to well resolve the hydrogen positions, due to its smaller density in comparison to atoms like C, N, O, and metals. Because of the relevant role of hydrogen interaction in biological systems,²⁵ in drug design it is mandatory to acquire information about the hydrogen acid-base interactions that our designed compounds could

perform. At this respect, different ss-NMR experiments, also allow us to study the acid – base interactions between the observed nuclei and its vicinity.^{26–29}

From the chemical point of view, acid-base interactions can be easily studied on the basis of the electron density distribution or the charge differences between interacting atoms or functional groups in the molecule. Fortunately, NMR spectroscopy (Dr. Florian's domain subject) is directly sensitive to the distribution of the electronic charge surrounding a nuclear site, this relationship is reflected by the chemical shift, as well as the quadrupolar interaction, that work as an approximation of the local electron density of an atom.^{30,31} Obtaining this data was relevant to understand our designed compounds because of, according to the Hard and Soft Acids and Bases (HSAB) principle (Dr. Méndez's domain subject), the metal (quadrupolar) sites of our molecules of interest are classified as Lewis acids and should react with a base depending on their polarizability. By the other hand, the quadrupolar interaction of each metal cation observed can then reflect its hard or soft behaviour as a Lewis acid.

The density functional theory (DFT), was useful to obtain the value of the hardness, softness and other reactivity parameters of our designed compounds. With this methodology, we studied the trends of our SOD -structure and activity-mimicking compounds, based on the changes of the electron density of the ligands to form stable coordination compounds with some metal cations and the relationship with their experimental and calculated NMR parameters.

2- Experimental details

Experimental work. Reagents and solvents were supplied by Baker, Fluka, Aldrich and Merck companies, and were used without any purification. IR spectra of the synthesized compounds, were obtained in the 4000-400 cm^{-1} region in a spectrophotometer Perkin Elmer Spectrum 400 by attenuated total reflectance at room temperature. Elemental analyses were done in a Perkin Elmer Precisely Serie II CN/O 2400 equipment, using cysteine as standard.

The electronic spectroscopy UV-Vis-NIR studies were performed by diffuse reflectance technique in solid state in the interval 4000 – 40000 cm^{-1} in a Cary-5E Varian spectrometer at 298K. Magnetic susceptibilities were determined using a Johnson Matthey MSB (model MK II 13094-3002) balance at room temperature and the De Gouy method. All those studies were done thanks to the support and collaboration of Dr. N. Barba-Behrens, FQ-UNAM, Mexico. The ss-NMR spectra were recorded in 750, 400, 300 and 200 MHz Bruker spectrometers using rotors of 2.5 and 1.3 mm and spinning frequencies of 10, 14, 30 and 60 KHz depending of the experiment. TMS, adamantane and alanine have been used as references for ^1H , ^{13}C , and ^{15}N respectively. The NMR spectrometers used are part of the Research Infrastructure - Magnetic Nuclear Resonance - Very High Fields group, at the CEMHTI-CNRS-Orléans.

Methyl imidazolic coordination compounds were obtained with a stoichiometric relationship 1:6 using inorganic salts of Co(II), Ni(II), Cu(II), Zn(II) and Cd(II), with the ligand 4(5)-methyl imidazole. For some products, single crystals were obtained and analyzed by X-ray diffraction (X-RD), which revealed its structure and some relevant intra e intermolecular interactions. The X-RD coordinates were used to perform first principle calculations of their NMR and reactivity parameters. For no crystallized compounds, their structure was obtained from the analysis of their experimental and calculated ss-NMR spectra, and using the structural proposal, their reactivity parameters were obtained.

Theoretical work. HSAB-DFT chemical reactivity parameters³²⁻³⁵ were calculated at the B3LYP/6-311+G(2d,2p) level of theory with Gaussian09 using their crystallographic coordinates. Electronic structure calculations were done in the clusters “ELECTROFILO” (FM cluster group) and YOLTLA (Universidad Autónoma Metropolitana-Iztapalapa). NMR parameters were calculated using CASTEP and MolecularStudio V.8.0 in the cluster ARTEMIS (Centre de Calcul Scientifiques en Région Centre (CCSC)- Université d’Orléans).

To identify and understand the reactivity of the ligand before and after coordination with the metal, the HSAB-DFT reactivity parameters and ^1H , ^{13}C , and ^{15}N ss-NMR spectra were obtained and analyzed. The analysis was performed looking for the relationship between reactivity and ssNMR parameters, and the structure of each compound.

3- Results and discussion

Experimental work. Twenty-two coordination compounds were synthesized by the use of inorganic salts of zinc (II), cadmium (II), cobalt (II), nickel (II) and copper (II) with the ligands 2-methyl imidazole and 4(5)-methyl imidazole. The compounds were characterized by elemental analysis, IR, UV-Vis-NIR and ss-NMR spectroscopy. For compounds which single crystals were obtained, their geometrical arrangement and structure were obtained by X-ray diffraction (**Figure 2**). The structure of no crystalline compounds, was solved based in the experimental and theoretical ss-NMR studies, elemental analysis and by the use of the previously reported analogous compounds to those expected. The geometries of the zinc (II) and cadmium (II) cations on the coordination compounds with 4(5)-methyl imidazole, were tetrahedral for both and showed similitudes in their ^{13}C experimental ss-NMR spectra, as well as in their theoretical study of their NMR parameters. The elemental analyses of the zinc (II) and cadmium (II) compounds were in accordance with the general formula $[\text{M}(\text{C}_4\text{H}_6\text{N}_2)]\text{X}_2$. The X-RD results of the coordination compounds of cobalt (II), nickel (II) and copper (II), revealed an octahedral geometry of the cation and from elemental analysis the general formulae $[\text{M}(\text{C}_4\text{H}_6\text{N}_2)_4\text{X}_2]$ for copper (II) compounds and $[\text{M}(\text{C}_4\text{H}_6\text{N}_2)_6]\text{X}_2$ for nickel(II) and cobalt (II) coordination compounds (M = transition metal and X = NO_3^- , Cl^- , Br^- , COO^- or SO_4^{2-} depending of the salt employed). Structural facts of arrangement and tautomerism of the ligand imidazolic rings, were revealed by the X-ray diffraction studied compounds. It was observed that, the tautomer 5-methyl imidazole (5-MeIz) of the ligand 4(5)-methyl imidazole, is the

preferred to coordinate the metals cations: Co(II), Ni(II), Cu(II), Zn(II) and Cd(II), under the reaction conditions. In the zinc (II) and copper (II) coordination compounds, an arrangement of two pairs of *trans* ligands, was observed. This orientation agrees with the structural preferences of the ligand previously

reported by Anderssons.³⁶ Additionally, the four ligands form a kind of propeller around the metal cation with angles between 5° to 16° in the *xy* plane.

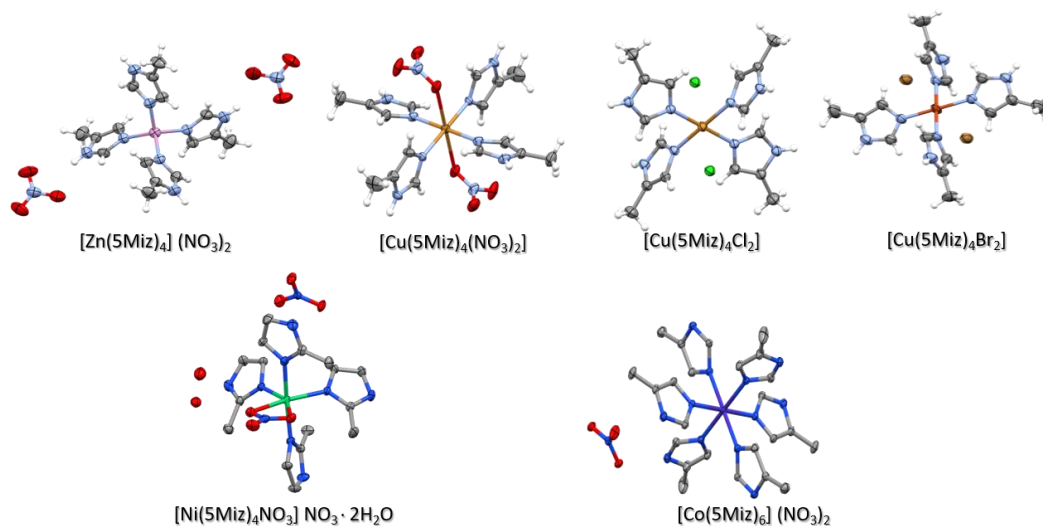


Figure 2. ORTEP diagrams from the X-ray diffraction results of the crystalline obtained compounds (ellipsoids at 30%)

The octahedral compounds of Co(II), Ni(II), and Cu(II), present a slightly octahedral distortion of elongation due to the Jahn-Teller effect but, the paramagnetism especially for cobalt (II) and copper (II) coordination compounds, is not significantly reduced (evidenced by the broad of the ss-NMR signals). The ss-NMR pulse sequences and conditions were selected for each compound according to their melting point, relaxation and the magnetism of the sample. For the zinc (II), and cadmium (II) compounds, their ¹H, ¹³C and ¹⁵N ss-NMR spectra were determined, for nickel (II) and cobalt (II) compounds ¹H and ¹³C was determined, meanwhile, for the copper complexes only ¹H ss-NMR spectra were determined. The paramagnetism of the cobalt (II) and copper (II) coordination compounds imposed some difficulties for the determination of the central transition and obtention of well-defined signals, which implies that we need to continue the optimization of the conditions to improve their spectra, avoiding the paramagnetic effects. No matter this late, ¹H ss-NMR spectra were useful to identify and correlates electron density changes reflected by first principle NMR and reactivity parameters.

Theoretical work. The analysis of calculated versus experimental solid state δ_{iso} values of the ligands: imidazole (Im), 2-methyl imidazole (2-MeIm) and 4-(5)-methyl imidazole (4-(5)-MeIm) shows that CASTEP and Gaussian09 provide good correlation factors, mainly for carbon ($R^2=0.98$ and $R^2=0.94$, respectively), and hydrogen ($R^2=0.84$ and $R^2=0.86$, respectively). For the nitrogen atoms, G09 present lower discrepancy with the experimental δ_{iso} . On the other hand, CASTEP represents in good agreement the intermolecular interactions between nitrogen atoms amino and imino. Using this validation of the calculated NMR parameters, CASTEP was used for the structural studies of no crystalline samples and G09 was used for the calculation of reactivity parameters.

Comparing the chemical reactivity of the imidazolic ligands, the trend of the global softness values 5-MeIm > 4-MeIm 2MeIm > Iz suggests that the methyl group slightly increases the density at the interior of the imidazolic ring from Iz to 5-MeIm. At local level, 4-MeIm behaves similar as Iz, in contrast to the symmetrical ligand 2-MeIz (considering its ability to perform hydrogen bonds). This

result confirms the previously reported proposal made by Anderssons³⁷ about the reactivity of the imidazolic ligands. Analyzing the acid-base interactions of the amino nitrogen atom (3N), its preference to be protonated follows the trend 2-MeIm > 4-MeIm > Iz > 5-MeIm.

The different δ_{iso} values obtained by ss-NMR spectroscopy for each nuclei observed, allow us, via the parameter σ , to get an evidence of the electron density distribution around the nuclei under study. Then we were able to correlate the experimental δ_{iso} values with the atomic chemical reactivity parameters for the atoms in the comparative ligands Imidazole, 2-methyl imidazole and 4(5)- metal imidazole, as well as for the coordination compounds. We obtained a linear regression factor of $R^2 = 0.90$ for the electrophilic reactivity of the carbon atoms in the ligands. It was found a good relationship between the carbon electrophilic reactivity and its isotropic chemical shift, as the electrophilic reactivity of the carbon atom increases its carbon δ_{iso} value decreases. For ^1H and ^{15}N , it was no correlation for nucleophilic, electrophilic or even radical reactivity.

The next step, was to analyze the diamagnetic coordination compounds obtained with 4(5)-MeIm and zinc (II) or Cd (II) nitrate, chloride and bromide salts because their diamagnetism did not provide magnetic difficulty to get good signals. In this case, the geometric analysis was followed according to the single crystals X-RD results for $[\text{Zn}(5\text{-MeIm})_4](\text{NO}_3)_2$. The optimization of the hydrogen atoms was performed with CASTEP and the δ_{iso} values and electric field gradient (EFG) were obtained for each compound. Those values were analyzed in joint with the HSAB-DFT reactivity parameters of each compound.

The HSAB-DFT global, local and condensed reactivity parameters of the ligands and the coordination compounds were obtained and allow us to understand the redistribution of electron density reflected by the σ parameter in the δ_{iso} observed for each nuclei analyzed. The reactivity parameters also reflected how the electron donor ability of the $-\text{CH}_3$ group changes the electron density distribution into the imidazolic ring of the ligand.

The condensed softness of the imino nitrogen atom (3N) in both tautomers of the 4(5)-Methyl imidazole ligand, showed a higher value in 5-MeIz than 4-MeIz, that probes the preference of tautomer 5-MeIz in the interaction with the metal cations in the complexes obtained. The reactivity of imidazolic ligands, free and in the coordination compounds, changes as well as the δ_{iso} for each molecule, showing the effect of the electron density redistribution.

The geometry of the $[\text{Cd}(5\text{-MeIm})_4](\text{NO}_3)_2$ coordination compound was in agreement with the theoretical (obtained by CASTEP) and experimental ss-NMR δ_{iso} based in the structural analysis and previous results obtained for $[\text{Zn}(5\text{-MeIm})_4](\text{NO}_3)_2$.

The condensed and local Fukui functions of the compounds for nucleophilic and radical attacks show that the nitrogen atoms (coordinated to the metal cations and the redox active cations) are the more reactive sites with a soft nucleophiles.

The changes on the V_{zz} parameter of the electric field gradient (EFG) calculated for the imino nitrogen atom of free and coordinated ligand, revealed that the V_{zz} value is less negative, as the electron donation π reduces. There is a reduction on the contribution of the imino nitrogen to the π density of the ring due to the increased σ donation to the metal and in consequence its charge is slightly increased. On the other hand, the orientation of the ligand is also related to the donor ability of the imino nitrogen atom and the asymmetry of V_{zz} . Considering the donation from the nitrogen atom to the metal cations, the electron donation is higher when the angle between the xy plane and the plane of the imidazolic ring is less than 15° . The diminishing of the π donation, according to the hardness of each 2+ cation, follows the trend: $\text{Zn} < \text{Cu} < \text{Ni} < \text{Co} < \text{Cd}$. Then, for the hardest cation Zn(II), the π donation of the imino nitrogen atom (of 5MeIm ligands) on its coordination compounds is less than the softer cation Cd(II) (its higher size enhances the retrodonation M-L).

4- Conclusion

We synthesized coordination compounds of methyl imidazole with copper(II), with structural similitude to the active site of CuZn-SOD and antioxidant activity that catalyze the dismutation of the superoxide anion. This study began with the analysis of the reactivity of the Me-imidazole ligands in terms of the methyl substitution and position to obtain coordination compounds with Zn(II), Cu(II), Ni(II), Co(II) and Cd(II). The reactivity of imidazolic ligands was analyzed and according to the HSAB-DFT reactivity parameters of the ligands and their ss-NMR spectra, as an evidence of the electron density distribution, it was corroborated that the methyl substitution and position modified the sigma donation ability of the imino nitrogen (3N atom) and the reactivity of the carbon atoms, impacting the pi acceptance ability of the ligands and stability of the coordination compounds. In concordance with Javadian and Araghi,³⁸ the imino nitrogen of the 5-MeIm ligand, loses π density, and increases its σ donation to form the coordination compound. This effect was reflected by the δ_{iso} in ^1H , ^{13}C and ^{15}N ss-NMR spectra for the ligands and the coordination compounds. The global, local and condensed reactivity parameters supported the previously published proposals³⁷ about the reactivity similitude between the three ligands studied. The antioxidant ability of the copper(II) coordination compound was modulated by the electronegativity of the counteranion which usually forms hydrogen bonds in the structure in solid state and also allowed to conduct the electrodonation of the imino electron donating atoms. This changes in the electron density of the hydrogen atoms was followed in the ^1H ss-NMR spectra (the paramagnetism produced a broad signal, but the deconvolution of the spectra clarified the small change). Solid state NMR spectra for the Cu(II) and Co(II) coordination compounds needed to be improved in order to get better signals avoiding the paramagnetic effects.

This study provided valuable information about the relationship between chemical reactivity and ss-NMR parameters that can guide the design of new antioxidant compounds.

Some results of this research have been presented in the Réunion RMN Grand Bassin Parisien 2019 (Nantes, France, 10th, Dec, 2019) and in a scientific seminar at Institute de Transgenose -Immunologie et Neurogenetique Experimentale et Moleculaire (INEM) (14th January, 2020).

During my research stay at CEMHTI, I participated in the MOOC Spectroscopy course in the 4th section: Nuclear Magnetic Resonance with was published in the MOOC platform the 1st June, 2020. For this MOOC course, 3964 attendants (High school, Higher Technician's Certificate, Technological University Diploma, Bachelor, Master and PhD students), from 77 countries were subscribed.

This fellowship allowed me to attend to the Nuclear Magnetic Resonance school in Madrid, Spain (October, 2019) and the IR-RMN workshop about advanced methods for quadrupolar nuclei, at Univ. Lille (Nov. 18, 2019), as well as in the annual user meeting of IR-RMN THC (Univ. Lille, Nov. 19, 2019).

As part of my performed activities related to the support and reinforcement of the NMR Symposia in Mexico, I continued the organization and performing of the Pre-Symposium NMR course (Universidad Michoacana, Morelia, Michoacán-Mexico, 24th-25th, October, 2019), and the virtual conferences of the V Symposia of NMR to be held from 26th to 31st, October, 2020.

5- Perspectives of future collaborations with the host laboratory

The results obtained will allow us to write some scientific articles. The sanitary emergency, due to SARS-CoV-2, leads us to redesign the V Symposia of NMR (we are part of the organizing committee) to be held in Morelia Michoacán, Mexico, at 26th-30th, October, 2020. Ten virtual conferences and one round table will be imparted by the Google Meet platform. Ten international researchers will present the application and original development techniques to study and solve chemical and

structural problems. In the round table PhD students, involved in the development and application of NMR techniques, will discuss with the attendants the advantage and opportunities to get a master or PhD in nuclear magnetic resonance, developing opportunities and impacting future collaborative work between Mexican research groups and those of the attendant researchers.

Regarding the work in progress, the development of new ss-NMR strategies to improve the study of the paramagnetic compounds need to be continued. Additionally, the similitude between the molecular systems studied in this project and the main topics of interest for the researchers involved, allow us to develop a new collaboration for the obtention of novel coordination compounds, useful in the bioinorganic chemistry as well as in the material sciences areas (i.e. MOF's and ZIF's). The ability of both research groups in the synthesis, structural analyzes by solid state NMR and development of structure-reactivity relationships guide us through a long-term collaboration. This collaboration will be reinforced by the research stays of students and researchers, as well as for future thesis works. This interaction will reinforce the development of high-level researchers and professionals on the nuclear magnetic resonance in the chemistry and material sciences areas.

6- Articles published in the framework of the fellowship

Arlette Richaud, María J. López, Martha Mojica, Julio A. Alonso and Francisco Méndez, 'Dimerization of pentacyclopentacorannulene C₃₀H₁₀ as a strategy to produce C₆₀H₂₀ as a precursor for C₆₀'. *RSC Adv.*, 2020,10, 3689-3693. <https://doi.org/10.1039/C9RA09804F>.

Francisco Gabriel Granados-Martínez, Diana Litzajaya Garcia-Ruiz, José de Jesús Contreras-Navarrete, Jael Madaí Ambriz-Torres, Carmen Judith Gutiérrez-García, Nelly Flores-Ramirez, Arlette Richaud, Francisco Méndez, Bertha Aguilar, Orlando Hernández-Cristóbal, Lada Domratcheva-Lvova, 'Composite synthesis from carbon nanotubes and styrene oligomers, the functionalization and magnetic field effect

in their properties', *Journal of Materials Science: Materials in Electronics* 31 7461-7469 (2020) doi:10.1007/s10854-020-02968-w.

Accepted for publication: Gutiérrez-Hernández, Abelardo ; Richaud, Arlette; Chacon-Garcia, Luis; Cortés-García , Carlos ; Méndez, Francisco; Contreras-Celedón, Claudia; "The deep eutectic solvent choline chloride:*p*-toluenesulfonic acid and water favor the enthalpy-driven binding of Arylamines to Maleimide in the Aza-Michael addition". *Journal of Organic Chemistry* (ACS).

Submitted to the journal: Antioxidants (MDPI). "Electrophilic Modulation of the antioxidant activity of copper (II) imidazolic coordination compounds mimicking the CuZn-SOD active site: the counteranion effect". This submitted paper, reports part of the results obtained in this research project.

7- Acknowledgements

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